

support of grants from the National Institutes of Health grants 1RO1 CA57534 (Truncated *c-erbB* Receptors in Women with Ovarian Cancer) to Nita J. Maihle, CA09441-13 (Multidisciplinary Basic Research Training in Cancer) to the Mayo Foundation, and 1KO7 CA76170-01A1 (Soluble ErbB1 molecules as Tumor Biomarkers) to Andre T. Baron.” with “The disclosed invention was made with the support of grants from the National Institutes of Health.”

On page 1, line 18, replace the sentence, “The present invention also provides diagnostic methods for determining the presence of an ovarian carcinoma in the patient by assaying the concentration of soluble ErbB1 variants in a biological sample from a patient.” with the sentence, “The present invention also provides diagnostic methods for assessing the risk of ovarian cancer or for determining the presence of an ovarian carcinoma in the patient by assaying the concentration of soluble ErbB1 variants in a biological sample from a patient.”

On page 1, line 25, replace “*c-erbB1*” with “EGFR/ERBB1”.

On page 2, line 1, replace “Downwald” with “Downward”.

On page 2, line 3, replace “has” with “have”.

On page 2, line 4, replace “*c-erbB*” with “ERBB”.

On page 2, line 6, replace “1991” with “1990”.

On page 2, line 7, replace “20” with “90”.

On page 2, line 8, replace “ErbB1/EGFR” with “Epidermal Growth Factor Receptor (EGFR/ErbB1)”.

On page 2, line 11, replace “Maihle *et al.*, Proc. Nat’l. Acad. Sci., 88, 1825 (1991)” with “Lax *et al.*, Cell Regul. 2, 337 (1991)”.

On page 2, line 15, add, after “(Ullrich *et al.*, *supra*).”, “In addition, alternatively spliced mRNA’s from the EGFR/ERBB1 gene also encode soluble forms of this receptor.”

On page 2, line 22, replace “c erbB1” with “EGFR/ERBB1”.

On page 2, line 22, add, after “Hunts *et al.*”, “Somat”.

On page 2, line 23, replace “2.6-2.7” with “1.8-2.8”.

On page 2, line 24, replace “chicken and rat tissue” with “human, chicken, rat, and mouse tissues”.

On page 2, line 25, replace “*supra*” with “Proc. Nat’l Acad. Sci. USA, 88, 1825 (1991)”.

On page 2, line 25, add, after “(1990)”, “Flickinger *et al.*, Mol. Cell Biol., 12,883 (1991); Das *et al.*, Endocrinology 134,971 (1994); Rho *et al.*, Mol. Carcinogenesis 11, 19 (1994); Reiter and Maihle, Nucl. Acids Res., 24, 4050 (1996); Tong *et al.*, Endocrinology 137, 1492 (1996).”

On page 3, line 1, replace “the ErbB family of receptors have been” with “ErbB receptors (sErbB) are being”.

On page 3, line 11, replace “763” with “753”.

On page 4, line 9, replace “endothelial” with “epidermal”.

On page 4, line 14, replace “EGFR ErbB1” with “EGFR/ErbB1”.

On page 6, line 6, replace “is” with “are”.

On page 6, line 15, add, after “EGFR”, “and/or sEGFR”.

On page 6, line 19, add, after “soluble”, “and full-length”.

On page 7, line 11, add, after “urine”, “saliva, sputum, breast nipple aspirates,”.

On page 7, line 14, add, after “patient”, “with ovarian cancer”.

On page 7, line 23, add, after “increase”, “or decrease”.

On page 7, line 24, replace “In particular” with “For example”.

On page 7, line 24, replace “uses” with “used”.

On page 7, line 25, add, after “half-life of”, “ligands, such as”.

On page 8, line 1, add, after “patient.”, “Alternatively, the method may be used to decrease the circulatory half-life of these ligands by allowing cells to remove sErbB1-ligand complexes from the circulation by endocytosis and intracellular membrane transport.”

On page 8, line 2, replace “increasing” with “altering”.

On page 8, line 17, add, after “differentiation”, “and may play important roles in regulating development, wound healing, carcinogenesis, and tumor progression.”

On page 9, line 8, after “p60”, add “sEGFR”.

On page 9, line 17, after “p170”, add “EGFR”.

On page 9, line 19, after “p110”, add “sErbB1”.

On page 9, line 19, after “p170”, add “EGFR”.

On page 9, line 20, after “p110”, add “sErbB1”.

On page 10, line 10, replace “spliced.2.8” with “spliced 2.8”.

On page 10, line 12, replace “synthesizes” with “synthesize”.

On page 11, line 8, replace “=40” with “=144”.

On page 11, line 8, replace “=40” with “=88”.

On page 11, line 17, replace “endothelial” with “epithelial”.

On page 12, line 21, add, after “sEGFR”, “or sErbB1”.

On page 12, line 22, replace “that is not anchored to the membrane of a cell,” with “that does not harbor a transmembrane domain”.

On page 12, line 24, replace “organism” with “cell”, and add, after “origin”, “through a constituent peptide domain. However, SerbB1 may be embedded or attached to the cell membrane through other moieties such as lipids, carbohydrates, and/or proteins”.

On page 12, line 25, remove “, or” after “cell”, and add, after “cell surface”, “or released from the cell surface by other mechanisms”.

On page 13, line 3, replace “EGFR” with “sEGFR”.

On page 13, line 6, add, after “natural”, “or transformed”.

On page 13, line 12, remove “,” after “nucleic”.

On page 13, line 15, replace “biologically” with “biological”.

On page 13, line 21, replace “ice” with “mouse”.

On page 14, line 21, replace “ErbB1” with “EGFR/ERBB1”.

On page 14, line 23, add, after “but”, “the full-length transcript”.

On page 16, line 20, add, after “which”, “the”.

On page 17, line 2, add, after “factor”, “receptor”.

On page 17, line 19, replace “histological” with “stage, grade, histological and molecular”.

On page 17, line 25, replace “DNA” with “cDNA”.

On page 18, line 5, delete “inactive”.

On page 18, line 6, replace “EGFR” with “ErbB family members”, and delete the second “EGFR” and replace with “receptor”.

On page 18, line 6, replace the third “EGFR” with “ErbB receptors”.

On page 18, line 7, replace “EGFR” with “receptor”.

On page 18, line 8, replace “activity of the EGFR” with “and other signaling activities of

ErbB receptor tyrosine kinases”.

On page 18, line 16, replace “DNA” with “cDNA”.

On page 21, line 11, replace “technique” with “techniques”.

On page 22, line 3, replace “deoxyribonucleotidetriphosphates” with “deoxyribonucleotide triphosphates”.

On page 25, line 16, add, after “or”, “cellular”.

On page 29, line 15, delete one 5-space indent from beginning of sentence.

On page 30, line 11, replace “EGFR” with “sEGFR”.

On page 30, line 13, add, after “p60”, “sEGFR”.

On page 30, line 25, replace “is” with “are”.

On page 31, line 1, add, after “e.g.”, “a peptide encoded by”.

On page 31, line 11, remove “the” before “p110”.

On page 31, line 12, add, after “p110”, “sEGFR”.

On page 32, line 22, add, after “urine,”, “saliva, sputum, breast nipple aspirates,”.

On page 32, line 23, replace “after” with “After”.

On page 34, line 5, remove “below”.

On page 34, line 17, replace “c-erbB1” with “EGFR/ERBB1”.

On page 34, line 22, replace “1” with “2”.

On page 35, line 1, replace “1986” with “2086”.

On page 35, line 17, replace “represented” with “encoding”, and after, p110, replace “cDNA” with “sEGFR”.

On page 35, line 22, replace “MM” with “mM”.

On page 35, line 25, replace “EXI5F and EXI5R” with “pEXI5F (SEQ ID NO:9) and pEXI5BR (SEQ ID NO:13)”.

On page 36, line 2, delete “RNA represented by”.

On page 36, line 4, add, after “3.0 kb”, “alternative”.

On page 36, line 13, delete “(p110) (SEQ ID NO:1)”.

On page 36, line 13, delete second “amino”.

On page 36, line 14, delete first “acids”.

On page 36, line 19, delete five-space indent before “Therefore”.

On page 36, line 24, replace “c-erbB1” with “EGFR/ERBB1”.

On page 36, line 25, replace “transcript” with “EGFR/ERBB1”.

On page 37, line 1, replace “681” with “705”.

On page 37, line 1, delete “after cleavage of the signal peptide”.

On page 37, line 5, add, after “EGFR”, “plus an additional 78 unique carboxy-terminal amino acids”.

On page 37, line 5, add “plasmid” before “pDR2241”.

On page 37, line 6, replace “sErbB1” with “EGFR/ERBB1”; replace “encodes” with “synthesizes”.

On page 37, line 6, replace “polypeptide (p110) that has ErbB1 ligand binding subdomains I through IV plus an additional 78 unique carboxy-terminal amino acids” with “glycosylated polypeptide (p110 sErbB1)”.

On page 37, line 9, replace “Curren” with “Current”.

On page 37, line 12, replace “reused” with “rinsed”.

On page 37, line 14, replace “gCI” with “ $\mu$ CI”.

On page 37, line 25, delete “As predicted,” and capitalize “I” on immunoprecipitation”.

On page 38, line 1, add “cell lysates from” before “transfected”.

On page 38, line 5, replace “mammalian” with “eukaryotic”.

On page 38, line 10, replace “c-erbB1” with “ErbB1”.

On page 38, line 26, replace “produces” with “encodes”.

On page 38, line 27, delete “we used”.

On page 39, line 9, delete “(Figure 7A)”.

On page 39, line 18, add “may” before “route” and replace “and that” with “whereas”.

On page 39, line 19, replace “will” with “may”.

On page 39, line 20, add “, which is” before “characteristic” and replace “results” with “may result”.

On page 40, lines 4, 5 and 6, delete “Cultures of ovarian carcinoma cells exposed to sEGFR preparations have reduced growth rates compared to cells which are not exposed to sEGFR. Thus, sEGFR can inhibit carcinoma cell proliferation.”

On page 40, line 24, replace “(MAb)” with “(MAbs)”.

On page 41, line 4, replace “compete” with “complete”.

On page 41, line 15, delete (MAbs).

On page 41, line 23, replace “ErbB1” with “sErbB1”.

On page 41, line 25, replace “ErbB1” with “sErbB1”.

On page 42, line 5, replace “Accession Nos. \_\_\_, \_\_\_, \_\_\_, and \_\_\_” with “HB-12204, HB-12205, HB-12206, and HB-12207”.

On page 43, line 8, replace “as well as to demonstrate that serum samples of healthy men and women contain a sErbB1 analog of approximately 110 kD (See Figure 14)” with “and in patients with ovarian cancer”.

On page 44, line 19, replace “c-erbB1” with “EGFR/ERBB1”.

On page 44, line 24, replace “c-erbB1” with “EGFR/ERBB1”.

On page 45, line 1, replace “c-erbB1” with “EGFR/ERBB1”.

On page 45, line 6, replace “c-erbB1” with “EGFR/ERBB1”.

On page 45, line 7, replace “c-erbB1” with “EGFR/ERBB1”.

On page 45, line 8, replace “c-erbB1” with “EGFR/ERBB1”.

On page 45, line 10, replace “c-erbB1” with “EGFR/ERBB1”.

On page 45, line 14, replace “(648)” with “(G418)”.

On page 46, line 11, replace “7.4,150” with “7.4, 150”.

On page 46, line 20, replace “FPLCO” with “FPLC”.

On page 47, line 10, replace “FPLCO” with “FPLC”.

On page 47, line 11, replace “FPLCO” with “FPLC”.

On page 47, line 20, remove right parenthesis before “10 mM”.

On page 47, line 23, insert right bracket after “Tween-20®”.

On page 49, line 1, replace “the subdomain” with “subdomain IV”.

On page 49, line 5, insert “and Characterization” after “Immunoprecipitation” and delete “and Characterization” at the end of line.

On page 49, lines 21 and 24, replace “FPLC®” with “FPLC”

On page 51, line 17, replace “ALISA, believed to be the same 110 kD protein isolated



from a human placental cDNA library as described above and is comprised of the 110 kD p110 sErbB1 SEQ ID NO. 2, and its variants” with “ALISA. Microsequence analysis of partially pure p110 sErbB1 from human serum using Matrix Assisted Laser Desorption/Ionization-Time of Flight Mass Spectrometry shows that this protein is derived from the 3.0 kb alternative transcript having SEQ ID NO. 2 of the invention.

On page 52, line 1, replace “appears to be less sensitive and accurate than the” with “differs substantially from the”.

On page 53, line 10, replace “00” with “60”.

On page 53, line 12, replace “< or > 00 IU/L, and LH level < or > 00 IU/L” with “<30 IU/L (premenopause) or >36 IU/L (postmenopause).”

On page 53, line 14, add “and” before “b”).

On page 53, line 16, delete right parenthesis after “facility”.

On page 55, line 12, replace “This” with “The”.

On page 56, line 18, replace “10 min.” with “10 min.,”.

On page 59, line 3, replace “(ù)” with “(ω)”.

On page 59, line 6, replace “Table 4” with “Table 2”.

On page 63, line 18, replace “Atairgin” with “TBIG”.